Docket No.: 2059-0103US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Harold G. BROWN et al.

Application No.: PCT/US00/02328

Filed: February 1, 2000

For: A PHARMACEUTICAL COMPOSITION OF COMPLEX CARBOHYDRATES AND ESSENTIAL OILS AND METHODS OF USING THE SAME

DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Karen K. Brown, B.S., Ph.D., do declare and say as follows:

I am a graduate of Washburn University, Topeka, Kansas and Oklahoma State University, Stillwater, Oklahoma.

My mailing address is c/o Dermal Research Laboratories, Inc., 5501 N.W. Foxhill road, Parkville, Missouri 64152.

I am presently employed by Dermal Research Laboratories, Inc., in the position of Chief Technology Officer (Partner & Secretary).

I am listed as one of the inventors of the subject of the above-identified application. I have read and I understand the prosecution history of the present application.

I have been conducting research on hyaluronic acid (hyaluronan or HA) since 1979. The initial test that I used for determination of molecular weight was intrinsic viscosity. Intrinsic viscosity has been the "gold standard" for determination of molecular weight of polymers and remains as such (still in use) today. Suppliers of HA report intrinsic viscosity on their Certificates of Analysis. Enclosed are Certificates of Analysis (Exhibits 1 and 2) for the Lifecore Biomedical product (listed in the specification on page 16, line 25+ of Applicants WO 00/44367.) and the Collaborative product (cited in Examples 25 and 26 of the present invention). They both list intrinsic viscosity which is the basis upon which I purchased (and still purchase) the HA for use in the present invention.

Throughout my research on HA, I developed several methods for molecular weight determination. One used the dextran standard. I found this standard to provide inconsistent results. I then switched to the protein standard which was more consistent than the dextran standard. The protein standard correlates directly to the intrinsic viscosity. Therefore, I consider the protein standard and intrinsic viscosity superior indicators for molecular weight determination of HA. This is not just my opinion but is shared by one of the leading HA researchers, Dr. Torvard Laurent. In a CIBA Foundation Symposium on "The Biology of Hyaluronan" (John Wiley and Sons 1989), the following question was asked by Dr. Warren Knudson: "Are there other standards besides HA oligosaccharides that would be easier to use for sizing HA, such as dextrans?" Dr. Laurent responds: "The calibration curves for dextran and hyaluronic acid and chondroitin sulfate are very different. You cannot use dextran." A copy of the cited page is attached as Exhibit 3.

For the research leading to the present invention, and at the time that I worked on the present invention, I purchased HA from suppliers that based molecular weight on intrinsic viscosity. At my laboratory, I tested the molecular weight of the HA based on the protein standard rather than the dextran standard.

Even in the Turley et al patent intrinsic viscosity is provided in the HA specifications that are cited. The intrinsic viscosity of the HA preparations that Turley et al cites range from 4.5 to

14.5 dl/g. An intrinsic viscosity of 14.5 relates to a molecular weight of approximately 750,000 daltons (actual = 747,870 daltons).

The intrinsic viscosity for the at least one fraction of high molecular weight HA cited in the present invention (>1,000,000 daltons) is >17.2 dl/g. Therefore, it is clear that the >1,000,000 dalton fraction in the present invention is outside the range taught by Turley et al.

The Examiner cites Turley et al (WO 97/25051, 1997) as disclosing a product comprising a hyaluronic acid fraction having a molecular weight in the range of about 30,000 to 2 million Daltons (page 5, lines 4-28). It should be noted that within this statement is the qualification on line 23-27 " detected by Dextran Standards (which corresponds to between about 9,000 daltons and about 600,000 daltons delivered by the Protein Standard using the conversion factor of about 3.3)." The claims of the current invention recite the composition as having at least one fraction with a molecular weight >1,000,000 daltons, which was measured using a protein standard and purchased on the basis of its intrinsic viscosity, the latter being a more universally used measurement of the molecular weight of polymers, including HA, and statistically correlates with the protein standard as shown in the graph below (Figure 1). Certificates of Analysis supplied with purchases of hyaluronic acid (prior to Turley et al and at present) list the intrinsic viscosity as a measure of the molecular weight.

Intrinsic viscosity is listed routinely in Turley where it appears that she is listing the testing reported on the Certificates of Analysis from her suppliers (see page 7, line 15, where the Intrinsic Viscosity is stated as 4.5 - 11 dL/g; page 8, lines 10-13, the Intrinsic Viscosity is stated as 10.0 and 14.5 deciliters per gram and the molecular weight based on the Intrinsic Viscosity is 500,000 to 800,000 daltons; page 9, lines 9-13, the Intrinsic Viscosity is between 11.5 and 14.5 deciliters per gram and the molecular weight is 600,000 and 800,000 daltons based on the Protein Standard and Intrinsic Viscosity; page 11, lines 18-19 a preparation from Lifecore™ Biomedical is described as having a Viscosity Average of <750,000 Daltons using a Protein Standard). In fact, every preparation cited identifies the Intrinsic Viscosity, Viscosity Average and/or Protein Standard.

Intrinsic Viscosity of HA is related to the molecular weight using the art-known Mark-Houwink Equation.

MW = (intrinsic viscosity*100/.036)^(1/.78)

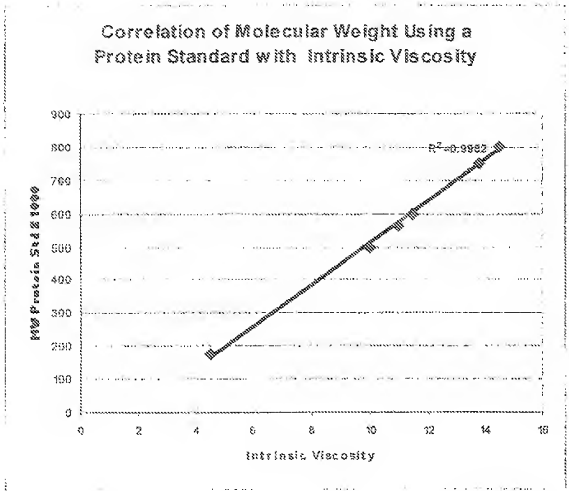
intrinsic viscosity = (MW^.78)*.036/100

Mark-Houwink Equation:

The preparations cited by Turley et al, demonstrated Intrinsic Viscosity values from 4.5 to 14.5 dl/g. Inserting the Turley et al intrinsic viscosity values into the Mark-Houwink Equation gives a molecular weight range for the Turley preparations between 166,857 and 747,870 daltons. This correlates well with the molecular weight range that Turley claims when basing her numbers on the protein standard.

When the intrinsic viscosity values and the molecular weight values (as determined using the protein standard) for the four sources of HA cited in Turley et al, are compared in a scatter chart, the result is the graph shown in Figure 1. The data used are listed next to the scatter chart. This graph demonstrates that the correlation between the molecular weight as measured using a protein standard and the intrinsic viscosity are statistically significant with a $R^2 = 0.9982$. A perfect correlation is 1.000.

Figure 1 Use of Turley et al Data to Demonstrate Correlation Between the Protein Standard and Intrinsic viscosity



Turley et al Data		
Source	Intrinsic Viscosity	MW Using Protein Standard
Hyal	4.5 11	178 562
2nd source	10 14.5	500 800
topical grade	11.5 14.5	600 800
4th source	13.8	750

The HA fraction >1,000,000 daltons claimed in the present invention would have an intrinsic viscosity of > 17.2 dl/g. The values in the present claims were measured using a protein standard which provides the same values as intrinsic viscosity.

Finally, on page 12, lines 11- 15, Turley clearly teaches away from use of molecular weights of 1,000,000 daltons or greater. "Recently, it has been found that large molecular weight hyaluronic acid having a molecular weight exceeding about 1,000,000 daltons, self-aggregates

and thus, does not interact very well with HA receptors. Thus, the higher molecular weight hyaluronic acid should be avoided (such as Healon™)".

Previously, the Examiner states that:

The molecular weight of the hyaluronic acid can range from 30,000 to 2,000,000 Daltons, thereby encompassing all of the molecular weight fractions recited in the rejected claims.

The Examiner's technical analysis confuses the protein and dextran standards. It is well known in the art that 30,000 to 2,000,000 Daltons using the dextran standard of Turley is well below the 1,000,000 dalton limitation using the protein standard. For instance, 2,000,000 Daltons using the dextran standard is about 650,000 Daltons using the protein standard. See page 25 of Turley.

The Examiner's attention is again directed to the Rule 132 Declaration attached to Applicants prior Reply. Indeed, the European Examiner was convinced by this Declaration and allowed the claims.

More specifically, as stated in the prior Rule 132 Declaration, for the research leading to the present application and at the time that the present application was prepared, I based the molecular weight measurements on the protein standard rather than the dextran standard. [The protein standard is easier to run and gives the same results as intrinsic viscosity.] The specific method used was size exclusion chromatography (gel permeation chromatography or HPLC) and the protein standards were Immunoglobulin M, with a molecular weight of 900,000 daltons, Thyroglobulin with a molecular weight of 670,000 daltons, Gamma globulin with a molecular weight of 158,000 daltons and Ovalbumin with a molecular weight of 44,000 daltons. Using this method, one of the complex carbohydrates used by applicants as an example of an effective high molecular weight component was confirmed to have a molecular weight greater than 1,000,000 daltons by a third party laboratory, using the same protein standards (see attached document titled "Certificate of Analysis No. 030791, Exhibit 4).

Indeed, Turley et al. teaches away from the present invention when she clearly states that a molecular weight >1,000,000 daltons will not be orally effective (see page 12, lines 8-14). In fact, Turley et al. teach away from using any composition with a molecular weight >1,000,000 daltons. In the present invention, one of the molecular weight fractions recited by the amended claims is >1,000,000 daltons.

I hereby declare that all statements made herein of my own knowledge are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 7/25/07 By: _____

Karen K. Brown, Ph.D.
Chief Technology Officer (Partner & Secretary)
Dermal Research Laboratories, Inc.

EXHIBIT 1

Final Product, SPEC 80081

Dried Sodium Hyaluronate, pH 4.0 Process

APPROVAL SIGNATURE

Dept/Date: Quality Control/5/14/1996	**Effective Date:** (Document Control Use Only)
QA/Date: 5/19/1996	Lot Number 2-1022-5

Purpose and Scope

To define the testing and specifications for Dried Sodium Hyaluronate, pH 4.0 Process, Medical Grade.

Chemical Structure

[-β-Sodium Glucuronic Acid-(1→3)-β-N-Acetyl Glucosamine-(1→4)-]$_n$

Acceptance Criteria

Test	Method	Specification
Intrinsic Viscosity	QATM 136	18.2 dl/g (MW 1.1 X 10^6)
Endotoxin	QATM 092	0.07 EU/mg NaHy maximum
Bioburden	QATM 208	≤ 100 cfu/g
Microbial Identification[1]	QATM 075	None of the following observed: *E. coli, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella sp.* & *Streptococcus pyogenes*
Water Content	QATM 256	≤ 10.0%
pH (1% solution in water)	QATM 021	6.2 -7.8
Osmolality (1% solution in water)	QATM 069	75 mOsm/kg maximum
Visual Appearance	QATM 071	White to off white, fluffy to small grain powder
Odor	QATM 071	None
IR Spectrum (4000-800 cm^{-1}) (1% solution in water)	QATM 081	Matches Standard
UV-VIS Spectrum (820-190nm) (1% solution in water)	QATM 086	Matches Standard
Nucleic Acid (1% solution in water)	QATM 086	A260 ≤ 0.5
Hyaluronidase sensitivity (1% solution in water)	QATM 065	Positive
Acetate Concentration	QATM 030	1.0 % maximum -- Meets Standard
Protein Concentration	QATM 001	0.1% maximum -- Meets Standard
Ethanol	QATM 229	0.5% maximum -- Meets Standard
Isopropanol	QATM 229	0.5% maximum -- Meets Standard
Methanol	QATM 229	0.25% maximum -- Meets Standard

Continued on next page

[1] Microbial identification is necessary only if microorganisms were found using QATM 208.

EXHIBIT 1

Acceptance Criteria (continued)

Test	Method	Specification
Arsenic	SOP 9011	2 ppm maximum -- Meets Standard
Cadmium	SOP 9011	5 ppm maximum -- Meets Standard
Chromium	SOP 9011	5 ppm maximum -- Meets Standard
Cobalt	SOP 9011	10 ppm maximum -- Meets Standard
Copper	SOP 9011	10 ppm maximum -- Meets Standard
Iron	SOP 9011	51 ppm maximum -- Meets Standard
Lead	SOP 9011	10 ppm maximum -- Meets Standard
Mercury	SOP 9011	10 ppm maximum -- Meets Standard
Nickel	SOP 9011	5 ppm maximum -- Meets Standard

Additional Information

Sampling Plan	Sample per MPR 0059 for QC Testing and Archiving
Storage Requirements	≤ -15°C
Retest Date	per SOP 0340

References

MPR 0059, Vacuum Drying and Packaging of Sodium Hyaluronate
QATM 001, Protein Assay
QATM 021, Hydrogen Ion Concentration (pH)
QATM 030, Acetic Acid Test
QATM 065, Hyaluronidase Test for Hyaluronan
QATM 099, Solution Osmolality
QATM 071, Sensory Testing for Raw Materials, In-Process, Final Products and NaHy Powder
QATM 075, Microbial Differentiation/Identification
QATM 081, Identification by Infra-red Spectroscopy
QATM 086, UV/VIS Scan and Optical Density
QATM 092, Photometric Endotoxin Assay
QATM 136, Determination of Intrinsic Viscosity and Average Molecular Weight
QATM 208, Aerobic Plate Count, Total Yeasts and Mold Count
QATM 229, Alcohol Quantification of NaHy Powder By Gas Chromatography With Headspace Sampler
QATM 256, Moisture Determination using MM710 Infrared Gauge
SOP 0340, Expiration Dating and Monitoring
SOP 9011, Outside Lab Testing of Materials

EXHIBIT 2

Collaborative Laboratories
Specifications Sodium Hyaluronate

Food grade. No animal origin materials used to produce this product.

Dynamic viscosity at + 25°C (1.0 % gel in water, dried basis): 9000 to 45000 cps (Brookfield viscometer LV DVI, Spindle N° 3, speed 1.5 RPM). HA in powder form.

CONTROLS	SPECIFICATIONS	SOP
Routine controls required by the customer		
. Characters	White powder, sparingly soluble to soluble in water, practically insoluble in acetone, in ethanol and in ether.	
. Identification (IR spectrum)	Complies	Collab-022
. Identification (sodium)	Positive	Collab-075
. Appearance of the solution (1.0 % solution, dried) Absorbance 600 nm	Clear ≤ 0.050 (*)	- Collab-003
. pH (1.0 % AH Na in water, dried)	6.0 to 8.0 (*)	Collab-009
. Intrinsic viscosity at 25°C (Ubbelohde, EP method)	20.00 to 26.00 dl/g (*) 1.1 to 1.6 x 10^6 Dalton	Collab-021
. Dynamic viscosity at + 25°C (1.0 % aqueous solution / dried basis – Brookfield viscometer LV DVI, Spindle N° 3, speed 1.5 RPM)	9 000 to 45 000 cps (**)	Collab-011
. Nucleic acid: Absorbance 260 nm (0.1 % solution, dried)	≤ 0.150 (*)	Collab-010
. Proteins	≤ 0.30 % (*)	Collab-012
. Chloride	≤ 0.3 % (*)	Collab-017
. Loss on drying	≤ 12.0 % (*)	Collab-007
. Total viable aerobic count	≤ 100 CFU/g (**)	Collab-004
. AH Na content (on dried)	95.0 to 105.0 %(*)	Collab-023
Scientific data collected on random batches (a minimum of 3 times per year)		
. Specific micro-organisms (Pathogens)	none observed	Collab-038
Note **Code: OGH**		

(*) Routine Testing
(**) Customer's requirements

Then comes a difficult phenomenon. At 'high' concentrations of CPC (>0.01 M) *small* molecular mass fragments may redissolve in CPC micelles after they have been precipitated. You can titrate HA by adding CPC, molecule for molecule to the solution, until complete precipitation. If you continue adding CPC, the precipitate dissolves—it is a detergent effect. One must avoid too large an excess of CPC when trying to precipitate oligosaccharides quantitatively at room temperature. Alternatively, you can lower the temperature of the solution to 4 °C, when the CPC crystallizes out, and among the crystals you find precipitated polyanion—even the low molecular mass material.

Warren Knudson: Are there other standards besides HA oligosaccharides that would be easier to use for sizing HA, such as dextrans?

Torvard Laurent: The calibration curves for dextran and hyaluronate or chondroitin sulphate are very different. You cannot use dextran (Laurent et al 1969).

Toole: In the area of the HA-binding proteins, molecular biological approaches will clarify many problems, as they are doing in other fields. Immunological cross-reactivity and peptide mapping will give us some information, but the DNA sequence gives the most information, particularly in determining whether there are 'families' of HA-binding proteins and in studying the regulation of expression.

Engel: I agree that molecular biology is needed in this field, but a more integrated approach is also needed. Cellular interactions with the extracellular matrix are so complicated that we miss a lot by just looking at one molecule. This applies for example to localization studies, where results from different laboratories are often difficult to compare. Therefore the localizations of a variety of important molecules should be studied simultaneously. It also applies to complex cellular assays. One may demonstrate that one molecule does this or that, but there might be another molecule that has an even more dramatic effect but is not being looked at.

Torvard Laurent: We certainly need a balance between studies of single substances and surveys of the integrated matrix structures. We have concentrated on one compound in this symposium, but there are other symposia dealing with the whole panorama.

As a final point, on the clinical side, are there any diseases with defective synthesis or defective degradation of hyaluronan? In Werner's syndrome, there is a high concentration of hyaluronan in serum and urine (for references see Laurent et al 1987); there may be other diseases.

Scott: There is a hydrocephalic mouse where, in sternal cartilage, Breen et al (1973) found more than 100% increase in HA, in the heterozygote. The homozygous hydrocephalic mouse had only 50% of the normal amount of HA. That is, there was hyaluronate increase in a fairly 'normal' animal.

Mason: With regard to degradative pathways, from Bryan Toole's work in early embryos, the changes in hyaluronan in tissues are so dramatic in effects on development that one suspects that if there were a defect, the em would not survive; so we may never find such a disease.

Torvard Laurent: I also expect that, but I am still fishing!

Toole: Andrew Copp and Merton Bernfield (1988) have been working mutant mouse where there is a decreased accumulation of hyaluronic ac specific areas of the embryo where deformities arise.

References

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EXHIBIT 3

Ciba Foundation Symposium 143

THE BIOLOGY OF HYALURONAN

A Wiley-Interscience Publication

1989

JOHN WILEY & SONS

Chichester · New York · Brisbane · Toronto · Singapore

EXHIBIT 3

Contents

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EXHIBIT 7

CAREF

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Centre d'Analyses et de Recherches Expérimentales de FOUGERES

CERTIFICATE OF ANALYSIS N° 030791

PRODUCT NAME: **SOLUTION OF SODIUM HYALURONATE**

Sample N° 110801-6

MANUFACTURER NAME: **Dermal Research Laboratories, Inc.**

Reference: Current European Pharmacopoeia.

CONTROLS	SOP	SPECIFICATIONS	RESULTS
. Proteins (2.5.16. - LOWRY method) (*)	CI-LAB-012	-	0.10 % (w/w)
. Proteins (BIURET method) (*)	Adapted CI-LAB-060	-	0.02 % (w/w)
. Size Exclusion Chromatography (2.2.30.)	CI-LAB-029		
- Average Molecular Weight (Mw)*		-	1.82×10^6 Dalton
- R ratio		-	0.580
- Polydispersity		-	1.50
- HA Na content valuation		-	0.91 % (w/w)
Quality Control Worker	*Analysis Laboratory Manager*		*Decision*
M. HAMELIN	M. DAVID		Date: 12/06/2003

(*) Protein standard: albumin bovine R for Protein determination
(*) Protein standards for Size Exclusion Chromatography (IgM, Thyroglobulin, Gamma Globulin, Ovalbumin)

Europäisches Patentamt | European Patent Office | Office européen des brevets

Urkunde Certificate Certificat

Es wird hiermit bescheinigt, dass für die in der Patentschrift beschriebene Erfindung ein europäisches Patent für die in der Patentschrift bezeichneten Vertragsstaaten erteilt worden ist:

It is hereby certified that a European patent has been granted in respect of the invention described in the patent specification for the Contracting States designated in the specification.

Il est certifié qu'un brevet européen a été délivré pour l'invention décrite dans le fascicule de brevet, pour les Etats contractants désignés dans le fascicule de brevet.

Europäisches Patent Nr. / **European Patent No.** / **Brevet européen n°**

1165097

Patentinhaber / **Proprietor of the Patent** / **Titulaire du brevet**

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WO 2000/044367 (03.08.2000 Gazette 2000/31)

(54) **A PHARMACEUTICAL COMPOSITION OF COMPLEX CARBOHYDRATES AND THEIR USE**

PHARMAZEUTISCHE ZUSAMMENSETZUNG AUS KOMPLEXEN KOHLENHYDRATEN DEREN ANWENDUNG

COMPOSITION PHARMACEUTIQUE D'HYDRATES DE CARBONE COMPLEXES L'UTILISATION DE CELLE-CI

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

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EP-A- 0 497 162	EP-A- 0 704 216
EP-A- 0 795 560	EP-A- 0 852 236
WO-A-90/00058	WO-A-92/18546
WO-A-92/22585	WO-A-93/05075
WO-A-93/09766	WO-A-93/11780
WO-A-95/23605	WO-A-95/34286
WO-A-96/05845	WO-A-96/32492
WO-A-97/25051	WO-A-97/33592
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DE-A- 19 547 105	US-A- 3 895 107
US-A- 4 585 656	US-A- 4 808 576
US-A- 5 773 425	US-A- 5 888 984

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- PATENT ABSTRACTS OF JAPAN vol. 016, no. 213 (C-0942), 20 May 1992 (1992-05-20) & JP 04 041431 A (SANTEN PHARMACEUT CO LTD), 12 February 1992 (1992-02-12)

EP 1 165 097 B1

Description

BACKGROUND AND FIELD OF THE INVENTION

[0001] The invention relates to a pharmaceutical composition for preventing and treating diseases and conditions of mammals associated with the adhesion, metastatic and coronary cascades comprising complex carbohydrates, which composition is applied orally or mucosally on a repeated basis and comprises complex carbohydrates as the sole active ingredient.

[0002] Complex carbohydrates, for purposes of this invention are defined as any polymer comprising more than two sugar moieties including such classes of compounds as polysaccharides and oligosaccharides. Polysaccharides include mucopolysaccharides and mannans whereas oligosaccharides are comprised of branched polysaccharides such as sialylated sugars including milk sugars.

[0003] Mucopolysaccharides are glycosaminoglycans which can be obtained from numerous sources (e.g. rooster combs, trachea, umbilical cords, skin, articular fluids and certain bacteria such as Streptococci spp). Most glycosaminoglycans (hyaluronic acid, chondroitin sulfates A, B, and C, heparin sulfate, heparin, keratan sulfate, dermatan sulfate, etc.) are composed of repeating sugars such as n-acetylglucosamine, glucuronic acid and n-acetyl galactosamine (these are known as non-sulfated glycosaminoglycans). If such glycosaminoglycans contain sulfur groups they are known as sulfated glycosaminoglycans.

[0004] Mannans are mannose-based polysaccharides which are normally extracted from plants. The most noteworthy is acemannan which is a beta 1,4-linked acetylated mannan extracted from the Aloe Vera plant (Aloe barbadensis Miller). This plant has been thought for centuries to have certain healing powers. Not until the 1980s was the active ingredient isolated and proven to have an effect on the immune system (see J. Pharm. Sci., 73 (1), Jan, 1984). Sialylated sugars are oligosaccharides which contain sialyl groups (e.g. sialic acid) and often contain fucose. Sialyl Lewis^x and its derivatives are examples from this group (Tyrell et al, Proc. Natl. Acad. Sci. USA, 88, Nov. 1991). At present, this oligosaccharide is so difficult to prepare/obtain that the cost is prohibitive and limits research activities to determine its mechanism of action. Some of the milk sugars (also called hexaoses) are also incorporated in this general class of compounds. Examples of these are difucosyllacto-N-hexaose a and b, Disialyl-monofucosyllacto-N-hexaose and monofucosyllacto-N-hexasose I, II, and II (obtainable from Oxford Glycosystems, Inc.).

[0005] Heparin, hyaluronic acid and chondroitin sulfate are the most studied complex carbohydrates. They fall in the class called mucopolysaccharides or glycosaminoglycans. Heparin has been used for a number of years as an anticoagulant. Hyaluronic acid has been used therapeutically since the 1970s as a replacement for the vitreous humor of the eye post surgery and, more recently, as replacement for joint fluid in arthritic joints. An extensive discussion of its various utilities is found in U.S. Pat. No. 4,141,973 to Balazs. The mode of action for hyaluronic acid injected directly into joints for treatment of arthritis has been proposed to be lubrication and replacement of the degraded joint fluid with highly viscous hyaluronic acid (see J. Bone Jt. Surg. 54A, 1972). High molecular weight (>1,000,000 daltons) and high viscosity have been reported to be critical. (For purposes of this application, all molecular weights are expressed as daltons. The unit designation will not be added hereafter.)

[0006] In the 1980s, it was discovered that chondroitin sulfate, or polysulfated glycosaminoglycan (known by its commercial name as ADEQUAN) could be injected intramuscularly for reduction of pain and inflammation associated with arthrosis of horses. The mechanism of action of this glycosaminoglycan has been speculated to be inhibition of certain degradative enzymes present in the joint fluid which are up-regulated by trauma.

[0007] In the 1990s, chondroitin sulfate had developed into a popular nutritional supplement being used extensively to treat joint disease. Such treatment requires oral doses between 1000 and 3000 mg/day of for humans. Even with these high doses, relief from joint pain often takes 6-9 months.

[0008] In 1989, it was discovered that intravenous, intramuscular or subcutaneous delivery of hyaluronic acid could reduce the pain of arthritis (U.S. Pat. No. 4,808,576 by Schultz et al) when the hyaluronic acid was delivered remote to the site of the arthritis (not into the joint). This patent specifically states that the hyaluronic acid is administered remote to the site and that the hyaluronic acid must be of high purity (>99% pure hyaluronic acid). Schultz et al. does not disclose or suggest the use of hyaluronic acid in combination with essential oils, use of other complex carbohydrate macromolecules, oral application or mucosal application. Schultz et al. specifically teaches away from use of low purity complex carbohydrates. By low purity is meant complex carbohydrates that would be considered food grade or cosmetic grade, which could be <98% pure and could contain such contaminants as endotoxins, lipoteichoic acids, proteins, nucleic acids, etc. The low purity hyaluronic acid or salt thereof useful in the present invention (<98% pure hyaluronic acid) can be of a cosmetic grade or food grade which can contain up to 5% contaminants. Such material would not pass the owl monkey eye test used to select high purity hyaluronic acids and salts thereof (described by Balazs in U.S. Pat. No. 4,141,973) in that it would produce an inflammatory response in the eye. It also would not pass the horse joint injection test described by Schultz et al (U.S. Pat. No. 4,808,576). However, it does not produce a reaction when applied to the skin or mucous membranes of mammals including humans, dogs, cats, horses, cattle, swine, rabbits, guinea pigs and

mice.

[0009] The importance of high molecular weight for effectiveness of hyaluronic acid in the treatment of arthritis is emphasized by Balazs (U.S. Pat. No. 4,141,973) and in a publication by Howard and McIlraith (see The Compendium, 15(3), March 1993) who summarize several clinical studies conducted to determine the most efficacious molecular weight range of hyaluronic acid injected intra-articularly to treat traumatic arthritis in horses. The conclusion from these studies is that hyaluronic acid with a molecular weight below 1×10^6 is not as effective as hyaluronic acid with a molecular weight above this value. More recently, della Valle et al (U.S. Pat. No. 5,166,331) claimed that there are two distinct pharmacologically active molecular weight ranges of hyaluronic acid or salts thereof. These moieties are utilized separately (purified one from the other) and defined as 50,000-100,000 (Hylastine) and 500,000-730,000 (Hylectin). Hylastine is specified for use in wound healing while Hylectin is specified for use in ocular surgery.

[0010] Whereas Balazs (U.S. Pat. No. 4,141,973), Schultz (U.S. Pat. No. 4,808,576) and della Valle (U.S. Pat. No. 5,166,331) all specify use of highly purified hyaluronic acid and whereas Balazs (U.S. Pat. No. 4,141,973) discards the fractions containing hyaluronic acid or their salts having molecular weights less than 750,000; and whereas della Valle (U.S. Pat. No. 5,166,331) discards impurities having molecular weights less than 30,000 and does not use hyaluronic acid with molecular weights between 100,000 and 500,000 and, thus, specifies use of clearly-defined molecular weights of hyaluronic acid for topical or ocular use; and whereas Schultz prefers use of hyaluronic acid with a molecular weight between 1.2×10^6 and 4.0×10^6 in topical formulations, we have discovered that all molecular weights of complex carbohydrates such as hyaluronic acids or salts thereof and all purities of these compounds are useful in oral or mucosal preparations for the treatment of numerous diseases and conditions.

[0011] The most recent studies on hyaluronic acid discuss treatment of various types of cancer with very large doses of this macromolecule (Falk, WO 97/40841). The Falk application suggests that doses should exceed 750mg. per 70 kg person, preferably, exceeding 1g. per 70 kg person. Such doses are given intermittently post diagnosis and are not suggested to be preventative or administered in low doses. Additionally, it is clear that the sodium hyaluronate of Falk needs to be pure enough for injection even though oral administration is used in addition to intravenous injection.

[0012] The Adhesion Cascade was first described in the early 1990s. In a summary by Adams and Shaw (The Lancet, 343, Apr. 2, 1994) the adhesion cascade which is stimulated when trauma occurs is divided into four sequential steps of tethering, triggering, strong adhesion and motility. Tethering interactions are mediated by a family of three lectin-like carbohydrate-binding molecules (selectins). These interactions are strong enough to cause the leukocytes to roll along the blood vessel walls to the site of trauma instead of flowing freely through such vessels, but not strong enough to cause these leukocytes to slow down. The triggering response is stimulated by factors such as cytokines and mediated by adhesion molecules called integrins. Integrins, by themselves, do not bind well to epithelium. However, when activated, integrins promote strong adhesion of the leukocyte to the epithelial surface. Leukocytes bind to the epithelial cells via their receptor sites such as CD44, CD31, etc. During strong adhesion, the interaction of these integrins with their ligands on the surface of the leukocytes are responsible for cessation of movement and flattening of the leukocyte. Finally, a process involving VCAM-1 and LFA-1 and other such integrins allows leukocytes to pass between endothelial cell junctions and into the tissue that has been traumatized. Collection of leukocytes at the site of trauma produces inflammation which is then followed by pain or other sequelae.

[0013] The present invention is based upon the premise that complex carbohydrates, including but not limited to glycosaminoglycans, bind to the receptor sites on leukocytes blocking their ability to tether to the blood vessel walls thus inhibiting the motility and interrupting the Adhesion cascade.

[0014] The metastatic cascade is very similar to the adhesion cascade. It has been proposed that tumor cells of all types contain CD44 receptor sites on their surface. These CD44 receptor sites appear to be involved in metastasis functioning similar to the receptor sites on leukocytes - tethering the tumor cells to the blood vessel wall and providing the motility necessary for movement from one site to another in the mammalian body. Once again, it is the premise of the present invention that complex carbohydrates, including but not limited to glycosaminoglycans, bind to the receptor sites on tumor cells blocking their ability to tether to the blood vessel walls and inhibiting the motility which, in turn, interrupts the potential for metastasis.

[0015] A Coronary cascade has recently been described in the Harvard Health Letter (December 1999, pg. 4-5). This cascade leads to the development of heart disease and stroke by causing plaque formation in the blood vessels. The theory is based on the premise that there are stable and unstable plaques produced on blood vessel walls. Unstable plaques are "swarming with T cells and macrophages" causing inflammation and make these plaques unstable. The T cells are described as sending macrophages a signal to release a protein called tissue factor which "spills out and encounters circulating blood, attracting platelets and triggers formation of a clot that quickly blocks up the artery". The compositions of the present invention are believed to inhibit the macrophages from infiltrating into the unstable plaques, thus preventing and treating heart disease and stroke.

[0016] It is unexpected that complex carbohydrates of the present invention could be administered orally or mucosally in low doses to inhibit the various cascades preventing and treating such a broad spectrum of diseases and conditions.

OBJECTS AND SUMMARY OF THE INVENTION

[0017] Although not bound by any theory, the invention relates to a pharmaceutical composition for preventing and treating diseases associated with the Adhesion and Metastatic cascades comprising complex carbohydrates, which composition is applied orally or mucosally on a repeated basis and comprises complex carbohydrates as the sole active ingredient.

[0018] More specifically, this invention describes a mechanism by which inflammation, including diseases and conditions associated therewith, tumor growth, tumor metastasis and/or allergies and allergy-related diseases can be prevented or treated.

[0019] It is understood that this invention describes the prevention and treatment of numerous diseases and conditions including but not limited to arthritis (osteoarthritis and rheumatoid arthritis), gastritis, colitis, esophagitis, bronchitis, sore throat, tonsillitis, tendonitis, fibromyalgia, sunburn, heat burns, temporomandibular joint (TMJ) condition, dental pain, itching associated with allergies and hypersensitivity, poison ivy, asthma, anaphylaxis, Attention Deficit Hyperactivity Disorder (ADHD), plaque formation associated with heart disease and stroke, increased degradation of spinal nerves post spinal cord injury, adhesion formation post surgery, scar formation post surgery, wound healing, decubutis ulcers, ganglion formation, Alzheimer's disease, HIV, cancer, Diabetes, skin problems such as acne, psoriasis, wrinkles, and even hair loss.

[0020] Such prevention and treatment are accomplished by orally or mucosally applying complex carbohydrates without essential oils to mammals in an amount and number of applications so as to be effective in preventing and treating the target disease or condition. It is proposed that such prevention or treatment results from blockage of the Adhesion, Metastatic, or Coronary cascades.

[0021] The delivery of these compounds to the site of trauma is accomplished by oral delivery of said compounds whereby the compounds are coated with protective oral delivery materials such as hydrogels, carbopols, etc., or delivered without a coating wherein the complex carbohydrates are the sole active ingredients(e.g. without the essential oil(s) being present as an active ingredient), and/or delivered mucosally wherein the complex carbohydrates are the sole active ingredients (e.g. without the essential oil(s) being present as an active ingredient).

[0022] Mucosal delivery includes but is not limited to application of the compounds to the mucous membranes of the nose, eyes, mouth, throat, gums, tonsils, eyes, esophagus, stomach, colon, rectum, vagina, or any other mucous membrane.

[0023] It is a further advantage of this invention that ultrapure or purified complex carbohydrates do not need to be used. Therefore, cosmetic or food grade complex carbohydrates, are acceptable for use to prevent or treat the above diseases or conditions if they are applied orally or mucosally. The preferred complex carbohydrates of this invention are mucopolysaccharides (glycosaminoglycans) including hyaluronic acid and salts, sulfates or derivatives thereof, chondroitin sulfate and polysulfated forms, salts or derivatives thereof, sialyl Lewis^x and salts or derivatives thereof, heparin and sulfates, salts or derivatives thereof, dermatan, and sulfates, salts or derivatives thereof, keratin and salts, sulfates and derivatives thereof, as well as combinations of the above. The most preferred complex carbohydrates are hyaluronic acid including salts, sulfates, esters, or derivatives thereof, chondroitin sulfate including polysulfated forms, low molecular weight heparin including salts, sulfates and derivatives thereof and sialyl Lewis^x including salts and derivatives thereof and combinations of the above.

[0024] It is an additional discovery that all sizes of complex carbohydrates are effective in this invention. Therefore, glycosaminoglycans, including chondroitin sulfate, heparin and hyaluronic acids of molecular weights <1,000, between 500,000 and 4,000,000, as well as above 4,000,000 are effective and non-reactive.

[0025] Additionally, it is a discovery that macromolecules (molecules with a molecular weight >1000) can be absorbed mucosally without the assistance of a delivery system and that said mucosally-absorbed macromolecules are effective at low doses.

[0026] Finally, it has been discovered that the Adhesion cascade which when stimulated by trauma, an allergen or other trigger mechanism which results in build up of leukocytes at the site of trauma or the trigger site can be blocked by delivering the complex carbohydrates of this invention .

[0027] Therefore, it has unexpectedly been found that essential oils when formulated with complex carbohydrates including polysaccharides, oligosaccharides, sialylated sugars, glycosaminoglycans or even monoclonal antibodies specific for the Adhesion or Metastatic cascades, can effectively treat the above-mentioned diseases and conditions when applied topically, orally, or mucosally.

[0028] Neither the complex carbohydrates nor the essential oils alone, when administered topically (e.g. topically as used in the present application does not include orally or mucosally) on the site of pain and inflammation, produce a significant preventative or therapeutic effect. However, when combined in the mixtures described herein, there is a definite therapeutic effect which can be felt within 30 minutes of the application.

[0029] Even more unexpectedly, it has been discovered that the complex carbohydrates alone can be applied orally or mucosally without essential oils to obtain an even better response (prevention or treatment) with a smaller dose.

[0030] This invention also encompasses a composition of matter comprising complex carbohydrate macromolecules as the sole active ingredient (e.g. without the essential oil(s) being present as an active ingredient), applied orally or mucosally to inhibit the Adhesion, Metastatic or Coronary cascades thus preventing or treating numerous diseases and conditions related thereto.

[0031] Macromolecules as used herein means any molecule with a molecular weight >1000. Mammals as used herein includes humans, dogs, cats, horses, cattle, swine, rabbits, guinea pigs, mice, and all other mammalian animals.

DETAILED DESCRIPTION OF THE INVENTION

[0032] As discussed above, there have been no previous investigations describing use of complex carbohydrates as the sole active ingredient (e.g. the without essential oil(s) being present as an active ingredient) to prevent and treat diseases associated with the Adhesion, Metastatic and Coronary cascades when delivered orally or mucosally, especially in low doses. By low doses is meant from 0.00005 mg/kg to 50 mg/kg, preferably from 0.005 mg/kg to 40 mg/kg, more preferably from 0.05 mg/kg to 20 mg/kg. The diseases and conditions that are preventable or treatable according to this invention (e.g. composition using the present active ingredient (complex carbohydrate) without essential oil(s)) include but are not limited to arthritis (osteoarthritis and rheumatoid arthritis), gastritis, colitis, esophagitis, bronchitis, sore throat, tonsilitis, tendonitis, fibromyalgia, headaches including migraines, pancreatitis, vaginitis, hemorroids, sunburn, heat burns, TMJ, dental pain, gingivitis, dental caries, post surgical pain, menstrual pain, anaphylaxis, pain prior to and during childbirth, itching associated with allergies and hypersensitivity, poison ivy, asthma, Attention Deficit Hyperactivity Disorder (ADHD), plaque formation associated with heart disease and stroke, increased degradation of spinal nerves post spinal cord injury, adhesion formation post surgery, scar formation post surgery, lack of wound healing, decubutis ulcers, irritation of nerve bundles, ganglion formation, Alzheimer's disease, HIV, cancer, Diabetes, skin problems such as acne, psoriasis, wrinkles, and even hair loss.

[0033] Finally, the invention describes a use for reducing the sequelae of trauma in irritated or inflamed tissue of mammals by oral or mucosal application of a complex carbohydrate or mixture thereof as the only active ingredient (e.g. without the essential oil(s) being present as an active ingredient).

[0034] Particularly amenable conditions for such prevention or treatment include but are not limited to irritated or inflamed muscles, cramped muscles, inflamed tendons, fibromyalgia, swollen and painful joints, bruised tissue, tired feet, allergic conditions of the skin, other allergic conditions including psoriasis, asthma, anaphylaxis, ADHD, open wounds, decubitis ulcers, burns, sunburns, inflamed stomach or intestinal lining (gastritis, colitis), dental problems, inflamed bronchi or esophagial lining, inflamed nerve bundles (ganglia), adhesions formed after surgery or trauma, post surgical pain, pain during and after childbirth, plaques formed on veins or arteries leading to heart disease and stroke, inflammation associated with Alzheimer's Disease, tumor formation and tumor metastasis.

[0035] A significant advantage of this invention is that pharmaceutical grade complex carbohydrates are not required. The invention preferably uses cosmetic or food grade complex carbohydrates. Such complex carbohydrates can be obtained from any source as long as the source is not contaminated with undesirable adventitious agents (disease-producing viruses, bacteria, fungi, parasites, etc.). For instance, cosmetic grade hyaluronic acid which is of low purity (containing up to 5% impurities such as proteins, nucleic acids, teichoic acids and endotoxins) costs approximately $2,000/Kg, whereas high purity pharmaceutical grade hyaluronic acid required for injection into mammals costs at least $100,000/Kg and contains less than 0.5% impurities. Low purity complex carbohydrates such as mucopolysaccharides may be contaminated with up to 5% wt/vol proteins, 5% wt/vol nucleic acids, 1% wt/vol teichoic acids, 5% wt/vol lipids, fractions of hyaluronic acid <30,000 (defined as reactive by both Balazs in U.S. Pat. No. 4,141,973 and della Valle in U.S. Pat. No. 5,166,331), 5% wt/vol endotoxins and other small molecules. Preferably "low purity" means containing up to about 5% impurities, more preferably from about 0.6-5% impurities, still more preferably from about 1-5% impurities. They will cause reactions when injected into monkey eyes or joints of horses but will not cause reactions when applied to the skin of mammals or when delivered orally or mucosally to such mammals. Because the pharmaceutical compositions of this invention are applied orally or mucosally, these contaminants produce no adverse reactions (e.g. irritation or blistering of skin). Additionally, if one must select and use only certain molecular weight ranges of hyaluronic acid or salts thereof, the cost would be prohibitive. In fact, the presence of multiple molecular weight fractions in compositions of the present invention is preferable for the efficacy.

[0036] In order to assure freedom from contaminating microorganisms, the formulations of this invention can include preservatives allowable in foods or topical preparations. Allowable preservatives include but are not limited to methyl and propyl parabens, propylene glycol, ethylenediamine tetraacetic acid (EDTA), sorbitol, ascorbic acid, sorbate and sorbic acid, benzoic acid, and any other acceptable preservative, including mixtures thereof. Preservatives that would not be allowable in oral or mucosal formulations include those that are know carcinogens such as formaldehyde, phenol, glutaraldehyde, and alcohols that are toxic to mammals (e.g. isopropyl, propyl, denatured alcohol).

[0037] All molecular weight ranges of complex carbohydrates are effective in formulations of this invention. For instance, hyaluronic acid with a molecular weight of <1,000, 1,000 to 30,000, 100,000 - 500,000, >1,000,000 or >4,000,000 have

proven to be effective. It has been found that complex carbohydrates, especially glycosaminoglycans with lower molecular weights (e.g. <50,000, preferably <30,000) act more quickly than those with high molecular weights (e.g. >1,000,000). However, the high molecular weight glycosaminoglycans provide a longer-lasting effect. It is believed that the latter macromolecules are broken down by enzymes in the body to smaller molecules. Therefore, there is a longer release of the more active smaller molecules producing a longer period of efficacy. Therefore, the preferred formulation includes a mixture of low and high molecular weight complex carbohydrates.

[0038] Complex carbohydrates, polysaccharides, glycosaminoglycans or their derivatives which bind to leukocyte receptor sites and/or bind to selectins, integrins, or any other receptor sites which are involved with the mechanism by which leukocytes move to sites of trauma or which enable metastasis of tumors and which, when bound, serve to inhibit any of the steps of the Adhesion or Metastatic cascades would be useful in such pharmaceutical compositions. Such compounds may be obtained from any source. They can be extracted from rooster combs (U.S. Pat. No. 4,141,973), produced by fermentation of bacteria (U.S. Pat. No. 4,782,046), or extracted from trachea, skin, umbilical cords, etc. and need only be pure enough to be used as a cosmetic in that they do not cause reactions when administered topically. These molecules include but are not limited to polysaccharides, glycosaminoglycans such as hyaluronic acids and derivatives or salts thereof (Genzyme, Lifecore Biomedicals, Meiji Seika Kaisha, Ltd.), chondroitin sulfates A, B, or C or their derivatives (SIGMA Chemical Company), keratan sulfate and derivatives thereof (SIGMA Chemical Company), heparin or heparin sulfate and derivatives thereof (SIGMA Chemical Company, Rhone Poulenc Rorer Pharmaceuticals), dermatan sulfate and derivatives thereof (SIGMA Chemical Company), mannans and derivatives thereof (SIGMA Chemical Company), acemannan (Carrington Laboratories) and derivatives thereof, extracts of the Aloe Vera plant and derivatives thereof (Aloe Vera gel concentrate supplied by Lily of the Desert, Irving, Tx.) and certain sialylated sugars such as trifucosyllacto-N-hexaose and sialyl Lewis^x (Oxford Glycosystems). The sources listed are exemplary only and not limitations of the invention.

[0039] It is a preferred embodiment of this invention that at least two molecular weight ranges of complex carbohydrates be included in the pharmaceutical composition. At least one should be from a low molecular weight range (from 1000 to <50,000 (e.g. 49,000)) and the other one or more should be from a higher molecular weight range (from 100,000 to 500,000 or >1,000,000). Such complex carbohydrates may or may not be a mixture of two or more different types of complex carbohydrates. For instance, one complex carbohydrate providing the high molecular weight moiety could be selected from the group consisting of hyaluronic acid and mannans and another complex carbohydrate in the same pharmaceutical composition providing the low molecular weight moiety could be a second polysaccharide or a sialylated sugar selected from the group consisting of chondroitin sulfate, keratan sulfate, heparin, heparin sulfate, dermatan sulfate, acemannan, sialyl Lewis^x, and hexaoses.

[0040] A more preferred embodiment would comprise a mixture of at least two polysaccharides in the pharmaceutical composition. One of these polysaccharides would be of a low molecular weight range of <30,000 (e.g. 1000-29,000) and one polysaccharide would be of a high molecular weight >1,000,000. An even more preferred embodiment of this invention comprises a mixture of equal parts of at least two polysaccharides. One of the polysaccharides would be of a low molecular weight range (<30,000). The second polysaccharide would of be a high molecular weight hyaluronic acid or salt or derivative thereof (>1,000,000).

[0041] The most preferred embodiment of this invention comprises equal amounts of two or more molecular weight ranges of hyaluronic acid or salts or derivatives thereof. Such a composition would comprise for instance, a hyaluronic acid or salt or derivative thereof with a low molecular weight of <30,000 combined with a hyaluronic acid or salt or derivative thereof which has a high molecular weight >1,000,000.

[0042] When heparin is used, it is advantageous to use low molecular weight heparin as it has been demonstrated to be free of anti-coagulant activity. However, it is expected that high molecular weight heparin will be broken down to low molecular weight heparin when administered orally or mucosally.

[0043] Complex carbohydrates which we have specifically utilized in successful pharmaceutical compositions include heparin, hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate, and acemannan (active ingredient of Aloe Vera).

[0044] The oral formulations of the immediate invention can include any of the complex carbohydrates, alone or in combinations without the presence of essential oil as an active ingredient, whereby the formulation is administered as a form selected from the group consisting of a liquid, an emulsion, a suspension, a cream, an ointment, a gel, a foam, a solid, a powder and a gum. It is contemplated that the liquid could be added to a drink or drink mix, to food, be a part of a soft drink, another type of carbonated drink, a supplement drink, used as a mouthwash or added to a mouthwash, as a toothpaste, as a gargle, as a spray, added to a vaporizor, as a liquid center of a gum or throat lozenge, or used in any other way so as to retain the effectiveness of the complex carbohydrate. A gel form could include a gel applied by mouth, to the gums, to the tongue, under the tongue, to the eyes, to the nose, to the vaginal area or vagina, or to the rectum. A foam could be added to wounds, to the mouth, to the gums, to the vagina or any other mucous membrane. A solid can be incorporated into food, treats such as candy or treats for animals, a chewing gum, a dissolvable gum, a lozenge, capsules, tablets, dissolvable tablets, suppositories and any other form that would not damage the effectiveness

of the complex carbohydrates.

[0045] Other additives may be added to said oral formulations to improve taste and palatability or enhance the flavor. For instance, treats for horses may include sugar or a liquid or gel may be applied to a sugar cube. Treats for dogs may include liver or yeast flavoring.

[0046] The same formulations as mentioned for oral use can be used for mucosal delivery of the complex carbohydrates. The only limitation is that the formulation remain in contact with a mucosal surface for a period of at least a few seconds, preferably between 5 and 10 seconds.

[0047] Although the complex carbohydrates may be added to foods which are then baked, it is preferred to add the complex carbohydrates to the surface of the food after baking is complete. This retains the greatest activity.

[0048] It is contemplated that the complex carbohydrates of the present invention may be added to nutritional supplements to enhance their effectiveness. For instance, a mixture of complex carbohydrates and zinc, zinc gluconate, zinc gluconate glycine could be used for more effective treatment of sore throat and colds. A mixture of the complex carbohydrates of this invention and capsaisin may produce an even more effective treatment for joint pain and swelling. Addition of vitamins, minerals and other nutritional additives may produce enhancement of the nutritional activity by the complex carbohydrates.

[0049] The present invention has been found to be particularly effective in the treatment of any type of inflammation, pain and/or itching which is associated with the Adhesion cascade defined and described earlier. It is preferable for treatment of muscle and joint inflammation and pain resulting from athletic injuries, treatment of inflammation and pain associated with arthritis and bursitis, and relief from pain often referred to as "tired feet", reduction of inflammation (edema) in extremities resulting from diabetes, reduction of inflammation and pain in addition to wound healing of decubitus ulcers resulting from poor circulation by diabetic patients or bedridden patients, treatment of inflammation and itching of skin resulting from allergic reactions such as poison ivy and insect bites/stings, treatment of inflammation and pain associated with tendonitis, treatment of inflammation and pain associated with muscle cramps, inhibition of bruising and inflammation post trauma or surgery if applied immediately, dissolution of bruises which have already formed, wound healing in superficial cuts and scrapes as well as wound healing after surgery to reduce scarring and adhesions, treatment of inflammatory skin conditions such as acne or psoriasis and treatment of dry skin, burns, or sunburn.

[0050] The most recent theories to explain heart attacks and stroke (Harvard Health Letter, December 1999, pgs 4 and 5, and SCIENCE vol:285, 23 July, 1999, pg 595-599) involves the eruption of unstable plaques which have been found to be infiltrated with T-cells and macrophages (leukocytes which cause inflammation) thus linking this disease syndrome to the Adhesion cascade. Therefore, it is expected that heart disease (heart attacks and stroke) can be prevented and treated with the complex carbohydrates of this invention. Therefore, it is expected that the complex carbohydrates of this invention can be used to prevent and/or treat heart disease. For example, it is contemplated that hyaluronic acid, salts or derivatives thereof could be taken daily as a preventative for heart disease, and/or stroke. Amounts from 1mg/day to 20 mg/day would be expected to prevent heart disease and stroke. This could be taken orally. Preferably, it would be taken mucosally. Alternately, a mixture of hyaluronic acid and chondroitin sulfate could be taken daily for prevention of heart disease and stroke. Again, the daily dose would be expected to be less than a total of 100 mg. Repeated low doses have been demonstrated to be between 0.0001 mg and 100mg.

[0051] The most recent theory to explain the significant neurological degeneration that occurs in Alzheimer's Disease involves a substantial inflammatory component (SCIENCE, vol: 286, 17 December, 1999, pgs 2352-2355) which appears to be related to the Adhesion cascade. Therefore, it is expected that the complex carbohydrates of this invention can be used to prevent and/or treat Alzheimer's Disease. For example, it is contemplated that hyaluronic acid, salts or derivatives thereof could be taken daily as a preventative for Alzheimer's Disease. Amounts from 1mg/day to 20 mg/day would be expected to prevent the degradation apparent in Alzheimer's Disease. This could be taken orally. Preferably, it would be taken mucosally. Alternately, a mixture of hyaluronic acid and chondroitin sulfate could be taken daily for prevention of Alzheimer's Disease. Again, the daily dose would be expected to be less than a total of 100 mg.

[0052] The most recent theory to explain the significant neurological degeneration that occurs after spinal cord injuries that leads to irreparable paralysis, is attack by the leukocytes rushing to the site of trauma (Adhesion cascade) to help repair the traumatized area, but instead, degrading the ends of the nerves in the spinal cord, fraying them which effectively inhibits their potential realignment and partial or complete repair . It is expected that paralysis resulting from spinal cord injuries could be prevented or treated effectively using the complex carbohydrates of this invention. In this case, since the patient may not be able to take an oral medication, the medication may be administered mucosally using suppositories (rectal or vaginal). The dose may need to be higher, in the range of 100 mg to 1,000 mg per day. It is also expected that drugs to assist repair of nerves would be administered concurrently.

[0053] The invention described herein is for use with any mammal including but not limited to humans, dogs, cats, horses, cattle swine, sheep, goats, etc.

[0054] The invention is further illustrated but is not intended to be limited by the following examples.

EXAMPLE 1

[0055] High molecular weight (>750,000) cosmetic grade hyaluronic acid obtained from Meiji Seika Kaisha, Ltd, was dissolved in distilled/deionized water (DI) to a concentration of from 1.1 to 1.5% wt/vol. This solution was treated with high pH and high temperature to break down the molecular weight to <30,000. The latter treatment involved raising the pH of the solution to 11.0 and mixing the hyaluronic acid at 37-60°C for at least 4 hours. The viscosity of a 1% solution measured at 37°C in a Cannon-Manning Viscometer dropped from >1000 c/s to <10 c/s as a result of this treatment. This hyaluronic acid was adjusted to 1.0% wt/vol by dilution in DI water. The 1.0% hyaluronic acid solution was aliquoted into 10 vials with 100 mL each. Various essential oils were added to each vial at a concentration of 2.0% vol/vol. The resulting suspensions were mixed at room temperature for 2-3 hours. The following essential oils were tested in this experiment: Rosemary Oil, Tea Tree Oil, Camphor Oil, Oil of Wintergreen, Eucalyptus Oil, Cinnamon Oil, Sage Oil, Jojoba Oil, Lemon Oil and Oil of Clove. All of the essential oils were obtained from Loranne Oils. All preparations were held at 4°C for 14 days after which they were evaluated for their suspension characteristics and for their sterility. Suspension characteristics were evaluated visually while sterility was evaluated by placing a 0.1 mL sample onto a blood agar plate, incubating the plate at 37°C for 7 days and observing the plates for the presence of colonies.

[0056] Tea Tree Oil, Eucalyptus Oil and Camphor Oil produced the best suspensions. These suspensions remained stable while the others separated out with the oil either dropping out or rising to the top of the hyaluronic acid solution.

[0057] Each suspension was remixed and aliquoted into 10 mL amounts in 25 mL vials. Five patients with localized chronic pain complaints were given one vial of each preparation over a period of 2 months. After using the first preparation, they were interviewed about effectiveness, safety (development of rashes or other adverse reactions), spreadability/feel and odor. Effectiveness was evaluated on a scale of 1 to 5 with 5 being the most effective (most relief of their condition). Safety was evaluated by noting any adverse effects. Spreadability was evaluated on a 1 to 3 scale with 3 being best. Odor was evaluated on a scale of 1 to 3. Pleasing was defined as 3 while unpleasing was given a value of 0. At this point, they were given the second preparation to evaluate. The third through 11th preparations were evaluated in the same manner. The 11th preparation contained hyaluronic acid without essential oils. Results are summarized in Table 1.

[0058] Interviews with all patients were positive in that all patients reported immediate relief within 5 minutes of applying the topical preparations. Two reported relief within 30 seconds of treatment. None of the patients reported that the hyaluronic acid alone was effective. None of the patients noticed untoward reactions. Spreadability was not ideal and most of the patients complained that the suspension was too thin and difficult to apply. However, they liked the fact that the preparations were not oily. The odors of the preparations were generally pleasing. Only Tea Tree Oil and Sage Oil produced "unpleasing" comments. All patients commented that even though the preparation had an odor at application, there was no residual odor noted within a few minutes after application.

[0059] The medical complaints of the patients being treated in this study included:

1. Chronic knee pain/swelling post knee surgery for chondromalacia
2. Chronic knee pain/swelling as a result of torn cartilage
3. Chronic pain/swelling in first and second finger of right hand diagnosed as arthritis
4. Chronic foot pain (undiagnosed)
5. Chronic pain in left thumb/wrist post reconstructive surgery

TABLE 1

EVALUATION OF COMBINATIONS OF ESSENTIAL OILS WITH LOW MOLECULAR WEIGHT HYALURONIC ACID

Oil	Effectiveness	Safety	Spreadability	Odor
Rosemary	5	No Rxs	2	3
Tea Tree	5	No Rxs	2	1.7
Camphor	4	No Rxs	1	3
Wintergreen	5	No Rxs	2	3
Eucalyptus	5	No Rxs	1.7	3
Cinnamon	4	No Rxs	2	3
Sage	4	No Rxs	1.7	1
Jojoba	4	No Rxs	1.7	1.7
Lemon	3	No Rxs	1.7	2
Clove	4	No Rxs	1.7	3

(continued)

EVALUATION OF COMBINATIONS OF ESSENTIAL OILS WITH LOW MOLECULAR WEIGHT HYALURONIC ACID

Oil	Effectiveness	Safety	Spreadability	Odor
None *	0	No Rxs	2	3

* Control - Contains only hyaluronic acid with no essential oils
No Rxs = No reactions observed by patients
The Effectiveness, Spreadability and odor scores are averages of the 5 responses.

EXAMPLE 2

[0060] High molecular weight (>750,000) cosmetic grade hyaluronic acid was obtained from Meiji Sieka Kaisha, Ltd. It was dissolved in distilled/deionized water (DI) to a concentration of 1.0 % wt/vol. The viscosity of this solution at 37°C was >1000 c/s and the molecular weight was >750,000. The 1.0% hyaluronic acid solution was aliquoted into 10 vials with 100 mL each. Various essential oils were added to each vial at a concentration of 2.0% vol/vol. The resulting suspensions were mixed at room temperature for 2-3 hours. The following essential oils obtained from Loranne Oils were tested in this experiment: Rosemary Oil, Tea Tree Oil, Camphor Oil, Oil of Wintergreen, Eucalyptus Oil, Cinnamon Oil, Sage Oil, Jojoba Oil, Lemon Oil and Oil of Clove. All preparations were held at 4°C for 7 days after which they were evaluated for their suspension characteristics and for sterility according to procedures described in EXAMPLE 1. All oils remained in suspension due to the viscosity of the hyaluronic acid. All of the preparations appeared sterile. Each suspension was remixed and aliquoted into 10 mL amounts in 25 mL vials. The same five patients with localized chronic pain complaints who evaluated the preparations in EXAMPLE 1 evaluated these preparations. At the same time that they were given the vials in Example 1, they were given the corresponding vial from this example. They were instructed to compare the two preparations with the same essential oil (denoted by numbers). After using the first preparation, they were interviewed about effectiveness, safety (development of rashes or other adverse reactions), feel (spreadability) and odor. Effectiveness was evaluated on a scale of 1 to 5 with 5 being the most effective (most relief of condition). Safety was evaluated by noting any adverse effect. Spreadability was evaluated on a 1 to 3 scale with 3 being best. Odor was evaluated on a scale of 1 to 3. Pleasing was defined as 3 while unpleasing was defined as 0. At this point, they were given the second preparation to evaluate. The third through 11th preparations were evaluated in the same manner. Results are summarized in Table 2. All numbers shown in this table are averages of the responses.

[0061] Patients indicated that although these preparations were as effective as the preparations in EXAMPLE 1, it took from 45 to 60 minutes for the effect to be significant. However, they indicated that the effect lasted for 4-8 hours. The effectiveness of preparations in EXAMPLE 1 seemed to last only 1-3 hours. All patients liked the spreadability of the preparations in EXAMPLE 2. All except the Camphor Oil spread smoothly and left the skin feeling soft. The Camphor Oil seemed to absorb rapidly leaving the skin feeling dry. Again, no adverse reactions were noted.
The complaints of the patients in this study included:

1. Chronic knee pain/swelling post knee surgery for chondromalacia
2. Chronic knee pain/swelling as a result of torn cartilage
3. Chronic pain/swelling in first and second finger of right hand diagnosed as arthritis
4. Chronic foot pain (undiagnosed)
5. Chronic pain in left thumb/wrist post reconstructive surgery

TABLE 2

EVALUATION OF A COMBINATION OF ESSENTIAL OILS WITH HIGH MOLECULAR WEIGHT HYALURONIC ACID

Oil	Effectiveness	Safety	Spreadability	Odor
Rosemary	4	No Rxs	3	3
Tea Tree V	4	No Rxs	3	1.7
Camphor	3	No Rxs	2	3
Wintergreen	4	No Rxs	3	3
Eucalyptus	4	No Rxs	3	3
Cinnamon	2	No Rxs	3	3
Sage	2	No Rxs	3	1
Jojoba	3	No Rxs	3	1.7
Lemon	2	No Rxs	3	2

(continued)

EVALUATION OF A COMBINATION OF ESSENTIAL OILS WITH HIGH MOLECULAR WEIGHT HYALURONIC ACID

Oil	Effectiveness	Safety	Spreadability	Odor
Clove	2	No Rxs	3	3
None *	0	No Rxs	3	3

*Control - Contains only hyaluronic acid with no essential oils
No Rxs = No Reactions
Effectiveness, Spreadability and odor scores are averages of the 5 responses.

EXAMPLE 3

[0062] A 1.0% wt/vol solution of dermatan sulfate (chondroitin sulfate B obtained from SIGMA Chemical Company) was prepared using DI water. The viscosity of this preparation was <10 c/s. The molecular weight was 15,000. This preparation was mixed 1:1 with the 1.0% wt/vol high molecular weight hyaluronic acid solution described in EXAMPLE 2. Five aliquots of 30 mL each were dispensed into vials. To the first aliquot was added 2.0% vol/vol Rosemary Oil. To vials 2-4 was added either Eucalyptus Oil, Wintergreen Oil or Tea Tree Oil (all obtained from Loranne Oils). No essential oils were added to the fifth vial. All preparations were held at 4°C for 7 days after which they were evaluated for their suspension characteristics. All oils remained in suspension due to the viscosity of the hyaluronic acid. Each suspension was remixed and aliquoted into 10 mL amounts in 25 mL vials. Three patients with chronic pain/swelling complaints were given one vial of each preparation to evaluate. They were asked to compare effectiveness, safety, spreadability and odor. The same numerical scales for evaluation of these parameters were used as is noted in EXAMPLES 1 and 2. Results are listed in Table 3.

[0063] The general response was that all preparations provided relief within 5 minutes and such relief lasted up to 6 hours. Also, spreadability was totally acceptable to all patients. It appears that this combination is more effective than the lower molecular weight preparation described in EXAMPLE 1 in that it provides both quicker and longer-lasting relief from pain. The control preparations containing only the essential oils did not provide relief and were not acceptable for spreadability. The control which contained only the dermatan sulfate and hyaluronic acid components ("NONE") was not effective.

The complaints of these patients included:

1. Chronic pain in left leg resulting from diagnosed osteoarthritis of the left hip
2. Chronic neck pain resulting from diagnosed stenosis and bone spur formation requiring surgery
3. Chronic tired feet (patient on feet on concrete floors all day)

TABLE 3

COMPARISON OF MIXTURES CONTAINING DERMATAN SULFATE, HIGH MOLECULAR WEIGHT HYALURONIC ACID AND VARIOUS ESSENTIAL OILS

Oil	Effectiveness	Safety	Spreadability	Odor
Rosemary	5	No Rxs	3	3
Eucalyptus	5	No Rxs	3	3
Wintergreen	5	No Rxs	3	3
Tea Tree	5	No Rxs	3	1.7
None *	0	No Rxs	3	3
Rosemary only **	0	No Rxs	0	3
Wintergreen Oil **	0	No Rxs	0	3
Tea Tree Oil **	0	No Rxs	0	1.7

* = Control - Contains only dermatan sulfate and hyaluronic acid with no essential oils
** = Contains only the listed essential oil and no hyaluronic acid
No Rxs = No reactions
Numerical values for effectiveness, spreadability and odor are averages of the 3 responses.

EXAMPLE 4

[0064] In order to determine whether a combination of a high and low molecular weight mixture of a salt of hyaluronic acid would produce results similar to those described in EXAMPLE 3, the following experiment was conducted. High molecular weight (>750,000) cosmetic grade hyaluronic acid (obtained from Meiji Seika Kaisha, Ltd.) was prepared as in EXAMPLE 2. The concentration of this solution was adjusted to 1.0% wt/vol. The viscosity of this solution at 37°C was >1000 c/s and the molecular weight was >750,000. Low molecular weight cosmetic grade hyaluronic acid (from the same source) was prepared as described in EXAMPLE 1. The resulting hyaluronic acid solution was adjusted to 1.0% wt/vol by dilution in DI water. Equal volumes of high molecular weight and low molecular weight hyaluronic acid solutions were mixed and aliquoted into 50 mL portions. To the first aliquot was added 2.0% vol/vol Rosemary Oil. To vials 2-4 were added either Eucalyptus Oil, Oil of Wintergreen or Tea Tree Oil, each at 2.0% vol/vol. No essential oils were added to the fifth vial. All preparations were held at 4°C for 7 days after which they were evaluated for their suspension characteristics. All oils remained in suspension due to the viscosity of the hyaluronic acid solution. Each suspension was remixed and aliquoted into 10 mL amounts. Three patients with chronic pain/swelling complaints were given one vial of each preparation to evaluate. They were asked to compare effectiveness, safety, spreadability and odor. The same numerical scales for evaluation were used as noted in EXAMPLES 1-3. Again, the results are listed as averages of the three responses. Results are listed in TABLE 4.

[0065] The general response was that all preparations provided relief within 5 minutes and such relief lasted up to 6 hours. Also, spreadability was totally acceptable to all patients. It appears that this combination is as effective as a mixture of low molecular weight dermatan sulfate and high molecular weight hyaluronic acid in that it provides quicker and longer relief from pain. The control preparations containing only the hyaluronic acid (NONE *) did not provide relief. The control preparations containing only essential oils (Tea Tree Oil or Wintergreen Oil) did not provide relief.

[0066] Patients generally commented that the preparations were not oily upon application, a quality that all appreciated. Also, all patients commented that although there is some odor upon topical application, there is no residual odor -- no odor could be detected by a few minutes after application.

The complaints of these patients included:

1. Chronic pain in left leg resulting from diagnosed osteoarthritis of the left hip
2. Chronic neck pain resulting from diagnosed stenosis and bone spur formation requiring surgery
3. Chronic tired feet (patient on feet on concrete floors all day)

TABLE 4

EVALUATION OF A MIXTURE OF HIGH AND LOW MOLECULAR WEIGHT HYALURONIC ACIDS

Oil	Effectiveness	Safety	Spreadability	Odor
Rosemary	5	No Rxs	3	3
Eucalyptus	5	No Rxs	3	3
Wintergreen	5	No Rxs	3	3
Tea Tree	5	No Rxs	3	1.7
None *	0	No Rxs	3	3
Tea Tree **	0	No Rxs	0	1
Wintergreen **	0	No Rxs	0	3

* Control - Contains only hyaluronic acids and no essential oils

** Contains only the essential oil listed but no hyaluronic acid

No Rxs = No reactions

Numerical scores for effectiveness, spreadability and odor are averages of the three responses

EXAMPLE 22

[0067] A 55 year old female who was known to be very susceptible to reaction to poison ivy was provided a mucosal composition comprising a mixture of high and low molecular weight sodium hyaluronate (as described in EXAMPLE 4) with no oils added. She had been helping other with cutting wood and noticed that there was a poison ivy vine wound around one of the logs that she was carrying in her bare arms. After completing the wood-cutting, she began taking the hyaluronate preparation orally. She took 10 mg in the morning and 10 mg at night for a period of 5 days. Twenty four hours after her exposure she noticed 2 "pinpoint" pustules on her arms. These never spread and disappeared by the third day. It is apparent by this example that oral glycosaminoglycans can prevent the development of an allergic reaction

such as a rash caused by poison ivy.

EXAMPLE 23

[0068] An 18 year old female suffered from chronic fibromyalgia of the face and neck. This condition had existed for approximately 5 years. There was nothing that provided relief for her condition. She was given a formulation containing a mixture of high and low molecular weight sodium hyaluronate (prepared according to EXAMPLE 4) to use orally. She took 10 mg two times per day (AM and PM). She reported that after only 1 day, her symptoms disappeared. She has continued to take the same dose for 6 months and has reported no return of her fibromyalgia. Therefore, a condition that has historically remained untreatable, is treatable with the compositions of the present invention.

EXAMPLE 24

[0069] A 9 year old male suffering from severe Attention Deficit Hyperactivity Disorder (ADHD) complicated by Turret's Syndrome, who was being treated by diet control with little success, was given a sample of the mixture used in EXAMPLE 23. He took 10 mg in the morning and 10 mg in the evening, using the solution as a mouthwash (holding it in his mouth for about 10 to 20 seconds and then swallowing). His parents kept very strict records of his activity and noted that his ADHD was fully controlled and he suffered no "tics" while taking the sodium hyaluronate. The one day that he forgot to take his morning dose he had a recurrence of his "tics" and became almost uncontrollable. However, within 15 minutes of his receiving the missing dose, he became calm and returned to normal. This boy has remained totally under control for 2 months. This has never been observed before, even when he was taking Ridlin. He had discontinued taking Ridlin 1.5 year before because of problems with side effects. The sodium hyaluronate has provided no adverse reactions or side effects.

EXAMPLE 25

[0070] A 60 year old male and 55 year old female (brother and sister) who routinely suffered severe sunburns the first few times that they were in the sun each summer, had been taking oral sodium hyaluronate gel for treatment of pain associated with a cervical disc stenosis (male) and chronic osteoarthritis of both knees (female). Pain from the conditions being treated was totally controlled by taking 5-10 mg twice per day. The sodium hyaluronate gel was prepared by adding sodium hyaluronate (Collaborative Laboratories, Inc) to a 1% concentration. This preparation had a molecular weight of >1,000,000. The gel was being applied directly on the tongue by dropper bottle. Both went on vacation together and spent most of 5 days in the bright sun in a boat. They did not use a sun blocker. Each previous year both had suffered severe discomfort from sunburn after the first day's exposure. This time, at the end of the 5 days, both noted that they were not sunburned, had suffered no discomfort and were developing a nice tan. It is believed that the preparation of this invention prevented sunburn, allowing tanning to occur.

EXAMPLE 26

[0071] A 60 year old male suffering from colon cancer had been unable to tolerate his colostomy and demanded that his surgeon reconnect his intestines. He refused chemotherapy but requested a preparation prepared according to this invention. He was given a formulation of sodium hyaluronate (Collaborative Laboratories, Inc) which was prepared with a mixture of molecular weights of hyaluronate (as in EXAMPLE 4). When he began taking the hyaluronate preparation, his CEA was 70.1. He has taken the hyaluronate at a dose of 10 mg three times per day mucosally and after 6 months of treatment his CEA has dropped to 4.1. He has taken no other treatments. This patient had also suffered from polymyositis for 15 years. For this he was taking 50 mg of Prednisone daily without much relief. He reported that after 1 week of taking the hyaluronate preparation he felt complete relief from the pain caused by his polymyositis. After 6 months he has been able to reduce his Prednisone to 5 mg per day. He physician has reported that his polymyositis has gone into remission.

EXAMPLE 27

[0072] A gum was prepared by mixing 100g of presweetened gum base with 10g of 1% high molecular weight (>1,000,000) sodium hyaluronate (Collaborative Laboratories, Inc.) and 2 mL of 100% Spearmint Oil. The gum was heated for approximately 10 seconds in a microwave until it was soft enough to knead in the glycosaminoglycan and essential oil. All components were kneaded together until a paste was produced. To the paste was added powdered sugar until the consistency was acceptable to cut into strips thus producing chewable gum. This gum, when chewed, dissolved within approximately 5 minutes and was used to treat the pain and inflammation of a sore throat, esophagitis,

tonsilitis, gastritis, headache, and arthritis. In all cases, the individuals being treated reported that the gum was effective in treating their condition or disease.

[0073] A more chewable gum can be produced by adding excipients which produce thickening. Also complex carbohydrates alone (e.g. without essential oil(s)) can be used in the various formulations to treat the conditions as described above also in the delivery systems as mentioned above. The latter composition of one or more glycosaminoglycans can be used alone or combined with other mucosally or orally safe drugs or compounds to obtain similar results.

EXAMPLE 28

[0074] A 54 year old female suffering from chronic osteoarthritis of both knees and spondylosis in the lower back, was attempting to control the pain in her knees and lower back by using Napralan (500 mg, BID), Pycnogenol (100 mg, BID), Glucosamine (750 mg, BID) and Chondroitin Sulfate (1000 mg, BID). Even on this regimen, there was a requirement for Depomedrol in the lower back approximately every 6 months. This individual presented suffering from sciatica associated with the spondylosis as well as severe pain and swelling in both knees, particularly in the left knee, which caused a noticeable limp (left knee). X-rays indicated that there was no cartilage remaining in either knee. She was asked what happened when she did not take the Glucosamine and Chondroitin Sulfate. She answered that she was almost unable to walk, certainly could not easily go down stairs. If the Pynogenol was also removed from the diet, the individual indicated that she could not tolerate the pain. She also reported that she had an active gastric ulcer that was controlled by taking 4 Pepcid AC per day. Initially, this patient was told to stop taking the Chondroitin Sulfate and Glucosamine and take 1.0 mL BID of liquid 1% sodium hyaluronate (10 mg) with an approximate molecular weight of 500,000 to 1,000,000. One day after starting this regime (without the Chondroitin Sulfate and Glucosamine) the patient reported feeling much better. She reported that she had no knee pain and her sciatica had disappeared. This patient continued the regimen and has been able to discontinue the use of the Pycnogenol as well. The patient reports a surprising improvement in her mobility. After taking the sodium hyaluronate for 2 years she is able to exercise by bicycling, walk without a limp and climb stairs easily. Unexpectedly, this patient has been able to discontinue taking the Pepcid AC and has had no exacerbation of her gastric ulcer and gastritis. Follow x-rays of her stomach have indicated a cure of her ulcer. It is believed that the mucosal glycosaminoglycan provided a soothing effect for the gastric ulcer as she reported an immediate improvement within one week of starting the mucosal hyaluronic acid. She was able to discontinue taking the Pepcid AC at that time.

EXAMPLE 29

[0075] The patient from EXAMPLE 28 had had extensive surgery on her left hand approximately 20 years prior to joining this experiment. The surgery had involved removal of a significant portion of the tissue structure of the hand, an abdominal flap and skin grafts. She had developed adhesions on the tendons of the hand and did not have much use of this hand prior to taking the preparation of this invention. Indeed, at the start of this experiment, the hand was so swollen from adhesion irritation that the structure of the hand could not be delineated. Within 9 months of beginning the mucosal hyaluronic acid treatment she noted that she could easily make a fist, that the swelling in the hand was non-existent and that the structure of the hand, including blood vessels, could now be seen. There was no more pain from the irritation of the adhesions. Follow-up with her reconstructive surgeon indicated that the adhesions were resolved. The surgeon was totally surprised - he had not seen such extensive adhesions resolve. It is apparent that preparations of this invention, when taken orally or mucosally can treat and prevent adhesion formation post surgery.

EXAMPLE 30

[0076] In order to determine whether low doses of other complex carbohydrates taken orally or mucosally could show effects similar to hyaluronic acid, 3 patients presenting with osteoarthritis, rheumatoid arthritis and dental pain were treated with chondroitin sulfate. The two patients with osteo and rheumatoid arthritis had been using chondroitin sulfate (1000 mg BID) and glucosamine (500 mg BID) with some reported success. They were instructed to discontinue taking these products and substitute the compositions of the immediate invention. A 5% (wt/vol) solution of chondroitin sulfate (Infinity Laboratories, Inc) without essential oil was prepared. This was dispensed into 30 ml bottles and provided to the three patients with instructions to take 1.0 mL orally BID, holding it in the mouth for approximately 10 seconds prior to swallowing it. This represented a dose of 5 mg BID. This provided relief within 15 minutes. However, the relief lasted only 3-4 hours. The patients reported that they had to take the chondroitin Sulfate solution three times per day to treat their pain. After two months of this regimen, the two arthritis patients were given a mixture of the 5% chondroitin sulfate and 1% high molecular weight hyaluronic acid. They were instructed to take this as often as necessary. Each reported that this product was effective when taken only 2 times per day and the effect lasted from 8 to 10 hours. This demonstrates that a mixture of low and high molecular weight complex carbohydrates is more effective and that significantly lower

doses (100 to 1000 fold less) of chondroitin sulfate are required for effective treatment of osteoarthritis and rheumatoid arthritis than are used in oral solid forms currently sold for these uses.

EXAMPLE 35

[0077] A 48 year old female singer who was suffering from chronic bronchitis (3 months) to the point that she was unable to sing was given a solution containing a mixture of a low and high molecular weight hyaluronic acid (Prepared as in EXAMPLE 4). She was told to take 5 drops morning and evening, holding it in her mouth for about 10 seconds before swallowing. This represented a dose of 5 mg twice per day (10 mg/day total). She reported that within 3 days of starting the oral/mucosal hyaluronic acid her sinuses began to drain profusely. This lasted for 2 days after which her bronchitis disappeared. She continued taking the hyaluronic acid for a period of 14 days and reported that her bronchitis had cleared up and she was, once again, able to sing.

EXAMPLE 36

[0078] A 46 year old female was taking mucosally-administered sodium hyaluronate prepared as in EXAMPLE 4 for treatment of bone spurs on her feet (ball and heal of both feet). She worked in retail sales and was on her feet on concrete floors for 8 hours each day. She reported that taking 10 mg twice per day allowed her to work comfortably each day.

[0079] Prior to taking the hyaluronic acid preparation of this invention, this patient had visited a hand surgeon to have a ganglion at the base of the middle finger on her left hand removed. It was the size of a pea and had been getting larger for the past 3 years. She had not been able to schedule surgery due to her work requirements. After taking the hyaluronic acid of this invention for a period of 3 months, she noticed that the ganglion was disappearing. By 5 months post initiation of mucosal hyaluronic acid, the ganglion was completely resolved. It appears that inflamed nerve bundles (ganglion) can be treated and prevented with the compositions of this invention.

[0080] Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may be limited by the claims.

Claims

1. A pharmaceutical composition for oral or mucosal delivery comprising as an active ingredient a pharmacologically effective amount of at least one complex carbohydrate selected from the group consisting of glycosaminoglycans, **characterized in that** the composition comprises at least one glycosaminoglycan having a molecular weight of greater than 1,000,000 dalton, with the proviso that said composition does not contain an essential oil as an active ingredient, the composition being in the form of a liquid, a gel, a solution, a suspension, an emulsion, an ointment, a cream, a solid, a powder, a gum, or a spray, and the composition further being part of or added to one of a drink, drink mix, soft drink, food, nutritional supplement, mouthwash, toothpaste, gargle, throat spray, vaporizer, chewing gum, dissolvable gum, throat lozenge, capsules, tablets, dissolvable tablets, treats, candy, gel, foam, powder, or suppositories.

2. The pharmaceutical composition according to claim 1, wherein said at least one complex carbohydrate is of low purity such that it would produce an inflammatory response in an owl monkey eye test but would not produce an adverse reaction when applied to the skin or mucous membranes of mammals.

3. The pharmaceutical composition according to claim 2, wherein said at least one complex carbohydrate contains from 0.6 to 5% by weight of contaminants.

4. The composition according to claim 1 or 2, wherein the complex carbohydrate is a hyaluronic acid or salt or derivative thereof.

5. The pharmaceutical composition according to claim 1 or 2, wherein said glycosaminoglycan is selected from the group consisting of hyaluronic acid, heparin, heparin sulfate, low molecular weight heparin, dermatan sulfate, chondroitin sulfate, polysulfated glycosaminoglycan, keratan sulfate, salts thereof and derivatives thereof.

6. The pharmaceutical composition according to claim 1 or 2, wherein it comprises said high molecular weight complex carbohydrates and at least one low molecular weight complex carbohydrate having a molecular weight in the range of from 1,000 to less than 50,000 or of from 100,000 to 500,000 dalton.

7. The pharmaceutical composition according to claim 6, wherein the high molecular weight and low molecular weight complex carbohydrates differ by chemical structure.

8. The pharmaceutical composition according to claim 6, wherein said high molecular weight and low molecular weight complex carbohydrates range from two different size polymers of the same complex carbohydrates.

9. The composition of claim 2, wherein the at least one low purity complex carbohydrate contains less than 98% by weight hyaluronic acid.

10. The pharmaceutical composition of claim 1 or 2, wherein the active ingredient is present in an amount of at least 0.01% wt/vol, preferably in an amount of at least 1% wt/vol.

11. The pharmaceutical composition of claim 1 or 2, which comprises at least one complex carbohydrate selected from the group consisting of a mixture of high and low molecular weight ranges of low purity hyaluronic acid in a total concentration of between 0.5% and 3.0% wt/vol.

12. The pharmaceutical composition according to any one of claims 1 to 11, for use as a medicament for prophylactic or therapeutic application by oral or mucosal delivery.

13. The pharmaceutical composition of claim 12, for use as a pain-relieving composition.

14. The pharmaceutical composition of claim 12, for use as a tumor preventative or treatment composition.

15. The pharmaceutical composition of claim 12, for use in preventing or treating inflammation, pain, tumor development and metastasis or allergy-related diseases and conditions of a mammal.

16. The pharmaceutical composition of claim 12, for use in preventing or treating inflammation, pain, tumor development and metastasis or allergy-related diseases and conditions selected from the group consisting of arthritis, bursitis, athletic injuries, trauma, anaphylaxis, surgery, childbirth, gastritis, colitis, esophagitis, bronchitis, sore throat, tonsillitis, tendonitis, fibromyalgia, TMJ, dental pain, bruising, poor circulation, muscle cramps, tired feet, allergies, poison ivy, insect bites/stings, asthma, sunburn, burns, edema related to diabetes, decubitus ulcers, superficial cuts and scrapes, open wounds, dry skin, psoriasis, Attention Deficit Hyperactivity Disorder (ADHD), plaque formation associated with heart disease and stroke, increased degradation of spinal nerves post spinal cord injury, adhesion formation post surgery, scar formation post surgery, wound healing, ganglion formation, Alzheimer's disease, HIV, cancer, wrinkles, and hair loss.

17. The pharmaceutical composition of claim 12, for use in the treatment of inflammation, pain or itching of a mammal.

18. The pharmaceutical composition of claim 12, for use in inhibiting the adhesion cascade.

19. The pharmaceutical composition of claim 12, for use in inhibiting tumor formation and tumor metastasis.

20. The pharmaceutical composition of claim 12, for use in preventing and treating diseases and conditions that are associated with the adhesion, metastatic or coronary cascades or that are related to allergies, wherein the composition comprises said complex carbohydrates as the sole active ingredient.

21. The pharmaceutical composition according to claim 20, wherein it comprises said sole active ingredient at a dose of between 0.0001 mg and 100 mg.

22. The pharmaceutical composition of claim 20 or 21, for use in preventing and treating diseases and conditions selected from the group consisting of arthritis, gastritis, colitis, esophagitis, bronchitis, sore throat, tonsillitis, tendonitis, fibromyalgia, sunburn, heat burns, temporomandibular joint (TMJ) condition, dental pain, gingivitis, itching associated with allergies and hypersensitivity, poison ivy, asthma, anaphylaxis, post surgical pain, childbirth, Attention Deficit Hyperactivity Disorder (ADHD), plaque formation associated with heart disease and stroke, increased degradation of spinal nerves post spinal cord injury, adhesion formation post surgery, scar formation post surgery, wound healing, decubitus ulcers, ganglion formation, Alzheimer's disease, HIV, cancer, Diabetes, skin problems such as acne, psoriasis, wrinkles, and hair loss.

Patentansprüche

1. Pharmazeutische Zusammensetzung für orale oder mukosale Abgabe mit einer pharmakologisch wirksamen Menge zumindest eines aus der Gruppe von Glykosaminoglykanen ausgewählten, komplexen Kohlenhydrats als Wirkstoff, **dadurch gekennzeichnet, dass** die Zusammensetzung mindestens ein Glykosaminoglykan enthält, das ein Molekulargewicht von über 1 000 000 Dalton besitzt, mit dem Vorbehalt, dass diese Zusammensetzung kein ätherisches Öl als Wirkstoff enthält, wobei die Zusammensetzung als Flüssigkeit, Gel, Lösung, Aufschlämmung, Emulsion, Salbe, Creme, Feststoff, Pulver, Gummi oder Spray vorliegt und die Zusammensetzung weiter Teil eines Getränks, einer Getränkemischung, eines Softdrinks, eines Nahrungsmittels, eines Nahrungsergänzungsmittels, eines Mundwassers, einer Zahnpaste, eines Gurgelwassers, eines Rachensprays, eines Vaporisers, eines Kaugummis, eines löslichen Gummis, eines Halsbonbons, von Kapseln, Tabletten, löslichen Tabletten, Leckereien, Bonbons, eines Gels, eines Schaums, eines Pulvers oder von Suppositorien ist oder einem von diesen hinzugefügt ist.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, worin das zumindest eine komplexe Kohlenhydrat von geringer Reinheit ist, so dass es eine entzündliche Reaktion in einem Augentest am Eulenaffen erzeugen würde, aber keine nachteilige Reaktion erzeugen würde, wenn es auf die Haut oder Schleimhäute von Säugetieren aufgebracht wird.

3. Pharmazeutische Zusammensetzung nach Anspruch 2, worin das zumindest eine komplexe Kohlenhydrat 0,6 bis 5 Gewichtsprozent an Verunreinigungen enthält.

4. Zusammensetzung nach Anspruch 1 oder 2, worin das komplexe Kohlenhydrat eine Hyaluronsäure oder deren Salz oder Abkömmling ist.

5. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin das Glykosaminoglykan aus der Gruppe von Hyaluronsäure, Heparin, Heparinsulfat, niedermolekularem Heparin, Dermatansulfat, Chondroitinsulfat, polysulfatiertem Glykosaminoglykan, Keratansulfat, deren Salzen und Abkömmlingen ausgewählt wird.

6. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin diese die benannten hochmolekularen komplexen Kohlenhydrate und zumindest ein niedermolekulares komplexes Kohlenhydrat mit einem Molekulargewicht im Bereich von 1000 bis weniger als 50 000 oder von 100 000 bis 500 000 Dalton enthält.

7. Pharmazeutische Zusammensetzung nach Anspruch 6, worin sich die hochmolekularen und niedermolekularen komplexen Kohlenhydrate in ihrer chemischen Struktur unterscheiden.

8. Pharmazeutische Zusammensetzung nach Anspruch 6, worin die hochmolekularen und niedermolekularen komplexen Kohlenhydrate von zwei Polymeren unterschiedlicher Grösse der gleichen komplexen Kohlenhydrate stammen.

9. Zusammensetzung nach Anspruch 2, worin das mindestens eine komplexe Kohlenhydrat niedriger Reinheit weniger als 98 Gewichtsprozent an Hyaluronsäure enthält.

10. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin der Wirkstoff in einer Menge von mindestens 0,01 % (Gew./Vol.), bevorzugt in einer Menge von mindestens 1 % (Gew./Vol.) vorliegt.

11. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, die in einer Gesamtkonzentration von 0,5 bis 3,0 % (Gew./Vol.) mindestens ein komplexes Kohlenhydrat enthält, das aus der Gruppe ausgewählt wird, die aus einer Mischung von hoch- und niedermolekularen Bereichen von Hyaluronsäure geringer Reinheit besteht.

12. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 11 zur Verwendung als ein Medikament zur prophylaktischen oder therapeutischen Anwendung durch orale oder mukosale Abgabe.

13. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung als eine schmerzlindernde Zusammensetzung.

14. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung als eine Tumoren verhütende oder behandelnde Zusammensetzung.

15. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung bei der Verhütung oder Behandlung von Entzündungen, Schmerzen, Tumorentwicklung und -metastase oder von allergiebezogenen Krankheiten und Leiden eines Säugetiers.

16. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung bei der Verhütung oder Behandlung von Entzündungen, Schmerzen, Tumorentwicklung und -metastase oder von allergiebezogenen Krankheiten und Zuständen aus der Gruppe von Gelenkentzündung, Schleimbeutelentzündung, Sportverletzungen, Sehnenentzündung, Trauma, Anaphylaxie, chirurgischen Eingriffen, Niederkunft, Magenschleimhautentzündung, Dickdarmentzündung, Ösophagitis, Bronchitis, Halsschmerzen, Mandelentzündung, Fibromyalgie, TMJ, Zahnschmerzen, Blutergüssen, Kreislaufstörungen, Muskelkrämpfen, müden Füssen, Allergien, Giftsumach, Insektenbissen und -stichen, Asthma, Sonnenbrand, Verbrennungen, Ödem bei Diabetes, Wundliegen, oberflächlichen Schnitten und Schürfungen, offenen Wunden, trockener Haut, Schuppenflechte, Aufmerksamkeitsdefizit-Hyperaktivitäts-Störungen (ADHS), mit Herzerkrankungen und Herzschlag verbundener Plaquebildung, verstärktem Abbau von Rückenmarksnerven nach Rückenmarksverletzungen, postoperativer Adhäsionsbildung, postoperativer Narbenbildung, Wundheilung, Ganglienbildung, Alzheimerscher Krankheit, HIV, Krebs, Falten und Haarausfall.

17. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung in der Behandlung von Entzündungen, Schmerzen oder Juckreiz bei einem Säugetier.

18. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung bei der Hemmung der Adhäsionskaskade.

19. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung bei der Hemmung von Tumorbildung und Tumormetastase.

20. Pharmazeutische Zusammensetzung nach Anspruch 12 zur Verwendung bei der Verhütung und Behandlung von Krankheiten und Zuständen, die mit den Adhäsions-, metastischen oder koronaren Kaskaden verbunden oder allergiebezogen sind, worin die Zusammensetzung die benannten komplexen Kohlenhydrate als einzigen Wirkstoff enthält.

21. Pharmazeutische Zusammensetzung nach Anspruch 20, worin diese den benannten einzigen Wirkstoff in einer Dosis zwischen 0,0001 mg und 100 mg enthält.

22. Pharmazeutische Zusammensetzung nach Anspruch 20 oder 21 zur Verwendung bei der Verhütung und Behandlung von Krankheiten und Zuständen aus der Gruppe von Gelenkentzündung, Magenschleimhautentzündung, Dickdarmentzündung, Ösophagitis, Bronchitis, Halsschmerzen, Mandelentzündung, Sehnenentzündung, Fibromyalgie, Sonnenbrand, Verbrennungen, Kiefergelenk- (TMJ-) Leiden, Zahnschmerzen, Zahnfleischentzündung, postoperativen Schmerzen, mit Allergien und Überempfindlichkeit verbundenem Juckreiz, Giftsumach, Asthma, Anaphylaxie, Niederkunft, Aufmerksamkeitsdefizit-Hyperaktivitäts-Störungen (ADHS), mit Herzerkrankungen und Herzschlag verbundener Plaquebildung, verstärktem Abbau von Rückenmarksnerven nach Rückenmarksverletzungen, postoperativer Adhäsionsbildung, postoperativer Narbenbildung, Wundheilung, Wundliegen, Ganglienbildung, Alzheimerscher Krankheit, HIV, Krebs, Diabetes, Hautproblemen wie Akne, Schuppenflechte, Falten und Haarausfall.

Revendications

1. Composition pharmaceutique destinée à une délivrance orale ou par les muqueuses comprenant en tant que principe actif une quantité pharmacologiquement efficace d'au moins un carbohydrate complexe sélectionné à partir du groupe constitué des glycosaminoglycanes, **caractérisée en ce que** la composition comprend au moins un glycosaminoglycane présentant une masse moléculaire supérieure à 1 000 000 daltons, à condition que ladite composition ne contienne pas une huile essentielle en tant que principe actif, la composition étant sous la forme d'un liquide, d'un gel, d'une solution, d'une suspension, d'une émulsion, d'une pommade, d'une crème, d'un solide, d'une poudre, d'une gomme, ou d'un nébulisat, et la composition faisant en outre partie de l'un d'une boisson, d'un mélange de boisson, d'une boisson sans alcool, d'un aliment, d'un supplément nutritionnel, d'un collutoire, d'un dentifrice, d'un gargarisme, d'un nébulisat pour la gorge, d'un vaporisateur, d'une gomme mâchable, d'une gomme pouvant se dissoudre, d'une pastille pour la gorge, de capsules, de comprimés, de comprimés pouvant se dissoudre, de friandises, de bonbons, de gel, de mousse, de poudre, ou de suppositoires ou étant ajoutée à ceux-ci.

2. Composition pharmaceutique selon la revendication 1, dans laquelle ledit au moins un carbohydrate complexe est

d'une pureté faible de sorte qu'elle produirait une réponse inflammatoire dans le test sur l'oeil de singe nocturne mais ne produirait pas de réaction indésirable lorsqu'elle est appliquée sur la peau ou sur les membranes muqueuses de mammifères.

3. Composition pharmaceutique selon la revendication 2, dans laquelle ledit au moins un carbohydrate complexe contient de 0,6 à 5 % en poids de contaminants.

4. Composition selon la revendication 1 ou 2, dans laquelle le carbohydrate complexe est un acide hyaluronique ou un sel ou un dérivé de celui-ci.

5. Composition pharmaceutique selon la revendication 1 ou 2, dans laquelle ledit glycosaminoglycane est sélectionné à partir du groupe constitué de l'acide hyaluronique, de l'héparine, du sulfate d'héparine, de l'héparine à faible masse moléculaire, du dermatane-sulfate, du chondroïtine-sulfate, du glycosaminoglycane polysulfaté, du kératane-sulfate, et de leurs sels et de leurs dérivés.

6. Composition pharmaceutique selon la revendication 1 ou 2, laquelle comprend lesdits carbohydrates complexes à masse moléculaire élevée et au moins un carbohydrate complexe à masse moléculaire faible présentant une masse moléculaire dans la plage allant de 1 000 à moins de 50 000 ou allant de 100 000 à 500 000 daltons.

7. Composition pharmaceutique selon la revendication 6, dans laquelle les carbohydrates complexes à masse moléculaire élevée et à masse moléculaire faible diffèrent par leur structure chimique.

8. Composition pharmaceutique selon la revendication 6, dans laquelle lesdits carbohydrates complexes à masse moléculaire élevée et à masse moléculaire faible comprennent deux polymères de taille différente des carbohydrates complexes identiques.

9. Composition selon la revendication 2, dans laquelle le au moins un carbohydrate complexe à faible pureté contient moins de 98 % en poids d'acide hyaluronique.

10. Composition pharmaceutique selon la revendication 1 ou 2, dans laquelle le principe actif est présent suivant une proportion d'au moins 0,01 % en poids/unité de volume, de préférence suivant une proportion d'au moins 1 % en poids/unité de volume.

11. Composition pharmaceutique selon la revendication 1 ou 2, qui comprend au moins un carbohydrate complexe sélectionné à partir du groupe constitué d'un mélange de plages de masse moléculaire élevée et faible de l'acide hyaluronique à faible pureté suivant une concentration totale comprise entre 0,5 % et 3,0 % en poids/unité de volume.

12. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, destinée à être utilisée en tant que médicament pour une application prophylactique ou thérapeutique par l'intermédiaire d'une délivrance orale ou par les muqueuses.

13. Composition pharmaceutique selon la revendication 12, destinée à être utilisée en tant que composition soulageant la douleur.

14. Composition pharmaceutique selon la revendication 12, destinée à être utilisée en tant que composition préventive ou de traitement de tumeur.

15. Composition pharmaceutique selon la revendication 12, destinée à être utilisée dans la prévention ou le traitement d'inflammation, de douleur, de développement et de dissémination métastatique de tumeur ou de maladies et d'états associés à l'allergie d'un mammifère.

16. Composition pharmaceutique selon la revendication 12, destinée à être utilisée dans la prévention ou le traitement d'inflammation, de douleur, de développement et de dissémination métastatique de tumeur ou de maladies et d'états associés à l'allergie sélectionnés à partir du groupe constitué d'arthrite, de bursite, de traumatismes sportifs, de tendinite, de trauma, d'anaphylaxie, de chirurgie, d'accouchement, de gastrite, de colite, d'oesophagite, de bronchite, de mal de gorge, d'amygdalite, de fibromyalgie, de syndrome d'articulation temporo-mandibulaire (TMJ), de douleur dentaire, de contusion, de circulation médiocre, de crampes musculaires, de pieds fatigués, d'allergies, de sumac vénéneux, de piqûres d'insecte, d'asthme, de coup de soleil, de brûlures, d'oedème associé au diabète, d'escarres

de décubitus, de coupures et d'écorchures superficielles, de plaies ouvertes, de peau sèche, de psoriasis, de troubles de déficit de l'attention avec hyperactivité (ADHD), de formation de plaque associée à des maladie et accident cardiaques, de dégradation accrue des nerfs spinaux après traumatisme de la colonne vertébrale, de la formation d'adhérence après chirurgie, de formation de cicatrice après chirurgie, de cicatrisation, de formation de ganglions, de la maladie d'Alzheimer, du virus VIH, de cancer, de rides, et de perte de cheveux.

17. Composition pharmaceutique selon la revendication 12, destinée à être utilisée dans le traitement d'inflammation, de douleur ou de démangeaison d'un mammifère.

18. Composition pharmaceutique selon la revendication 12, destinée à être utilisée dans l'inhibition de la cascade d'adhérence.

19. Composition pharmaceutique selon la revendication 12, destinée à être utilisée dans l'inhibition de la formation de tumeur et de la dissémination métastatique de tumeur.

20. Composition pharmaceutique selon la revendication 12, destinée à être utilisée dans la prévention et le traitement de maladies et d'états qui sont associés aux cascades d'adhérence, métastatiques ou coronaires ou qui sont associés à des allergies, où la composition comprend lesdits carbohydrates complexes en tant que principe actif unique.

21. Composition pharmaceutique selon la revendication 20, laquelle comprend ledit principe actif unique à une dose comprise entre 0,0001 mg et 100 mg.

22. Composition pharmaceutique selon la revendication 20 ou 21, destinée à être utilisée dans la prévention et le traitement de maladies et d'états sélectionnés à partir du groupe constitué d'arthrite, de gastrite, de colite, d'oesophagite, de bronchite, de mal de gorge, d'amygdalite, de tendinite, de fibromyalgie, de coup de soleil, de coups de chaleur, du syndrome d'articulation temporo-mandibulaire (TMJ), de douleur dentaire, de gingivite, de douleur post-chirurgicale, de démangeaison associée à des allergies et à une hypersensibilité, de sumac vénéneux, d'asthme, d'anaphylaxie, d'accouchement, de trouble de déficit de l'attention avec hyperactivité (ADHD), de formation de plaque associée à des maladie et accident cardiaques, de dégradation accrue des nerfs spinaux après traumatisme de la colonne vertébrale, de formation d'adhérence après chirurgie, de formation de cicatrice après chirurgie, de cicatrisation, d'escarres de décubitus, de formation de ganglions, de la maladie d'Alzheimer, du virus VIH, de cancer, de diabète , de problèmes de peau tels que l'acné, le psoriasis, les rides et la perte de cheveux.

INFORMATIONSBLATT / INFORMATION SHEET

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